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Prevention and management of idiosyncratic drug-induced liver injury: Systematic review and meta-analysis of randomised clinical trials

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ABSTRACT

Conducting randomised clinical trials (RCTs) in idiosyncratic drug-induced liver injury (DILI) is challenging. This systematic review aims to summarise the design and findings of RCTs in the prevention and management of idiosyncratic DILI. A systematic literature search up to January 31st, 2020 was performed. Recognised scales were used to assess methodological bias and quality of the studies. Quantitative and qualitative analyses were performed. Heterogeneity was assessed with I^2 statistic. Overall, 22 RCTs were included: 12 on prevention (n = 2,471 patients) and 10 in management (n = 797) of DILI/non-acetaminophen DILI-related acute liver failure (ALF). Silymarin (eight studies), bicyclol (four), magnesium isoglycyrrhizinate (three), *N*-acetylcysteine (three), tiopronin (one), L-carnitine (one), and traditional Chinese medicines (two) were tested in the intervention arm, while control arm mostly received standard supportive care or placebo. Main efficacy criteria in the prevention RCTs was DILI incidence or peak of liver enzymes value. In management RCTs, the efficacy parameter was usually 50 % decrease or normalisation of liver enzymes, or survival rate in DILI-related ALF patients. Overall, 15 trials described the randomisation method, eight were double-blind (n = 672) and nine had sample size estimation (n = 880). Four RCTs involving 377 patients used an intention-to-treat analysis. Based on the scarce number of trials available, tested agents showed limited efficacy in DILI prevention and management and a favourable safety profile. In conclusion, heterogeneity among studies in DILI case qualification and methodologic quality was evident, and the RCTs performed demonstrated limited efficacy of specific interventions. International research networks are needed to establish a framework on RCTs design and therapeutic endpoints.

Abbreviations: DILI, drug-induced liver injury; ALF, acute liver failure; NAC, *N*-acetylcysteine; MgIG, magnesium isoglycyrrhizinate; RCT, randomised clinical trial; ITT, intention-to-treat analysis; RR, relative risk; CI, confidence interval; anti-TB, anti-tuberculosis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TBil, total bilirubin; GGT, gamma glutamyl transferase; ULN, upper limit of normality; INR, international normalized ratio; CTCAE, Common Terminology Criteria for Adverse Events; WHO, World Health Organization; RUCAM, Roussel Uclaf Causality Assessment Method.

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1. Introduction

Idiosyncratic drug-induced liver injury (DILI) is an uncommon but potentially severe hepatic disorder presenting with an array of phenotypes and whose diagnosis is still one of exclusion. Due to the difficulties in collecting sizeable and homogenous cohort of patients, DILI remains a relatively orphan disorder from a therapeutic standpoint [1].

Management of DILI consists of a high level of suspicion and rapid discontinuation of the offending drug in combination with supportive treatment if necessary [2]. In the majority of DILI cases spontaneous recovery follows, but in a fraction of them acute liver failure (ALF) requiring liver transplantation or leading to death occurs [3]. Currently, no specific therapy has been approved for DILI treatment. Nonetheless, some therapeutic approaches, based on anecdotal observations, have been tested. Thus, cholestyramine has been tried to treat terbinafine-induced hepatotoxicity [4], whilst the use of carnitine has been shown in individual cases or case series to improve valproic acid-induced liver damage [5]. Similarly, the potential benefit of ursodeoxycholic acid as hepatoprotective agent for the management of pruritus in persistent cholestatic DILI is controversial [6–8].

Corticosteroids have long been used empirically in the management of some forms of DILI and more recently, with the rationale that adaptive immune system is involved in DILI pathogenesis [9]. However, in a retrospective analysis including 361 ALF patients, some of whom had DILI, treatment with corticosteroids failed to improve overall survival [10].

A prospective controlled trial conducted in the King's College Hospital concluded that the administration of *N*-acetylcysteine (NAC) improved survival in patients with fulminant hepatic failure after paracetamol overdose [11]. A post hoc analysis of a multicentre prospective study from the Acute Liver Failure Study Group involving 173 patients with ALF of various aetiologies, including DILI-related ALF, showed a beneficial effect of NAC treatment in those with grade I—II encephalopathy significantly improved transplant free survival management of ALF [12]. Conversely, two trials in paediatric population reported no efficacy of NAC [13,14]. In a retrospective, uncontrolled study the combination of NAC and prednisolone improved liver parameters in 21 patients with suspected severe DILI related to flupirtine [15]. Thus, conflicting results were shown in different, mostly underpowered studies, and these results await further validation.

Oxidative stress caused by reactive metabolites from drugs has been suggested as a pathological mechanism of liver injury [16–18]. Hence, a number of natural components exhibiting antioxidant properties both in animal models and *in vitro* experiments have received growing attention in the last years. These include silymarin, a natural compound present in species derived from *Silybum marianum* (commonly known as Milk thistle) [19,20]; bicyclol, a novel synthetic anti-hepatitis drug derived from diphenyl dimethyl bicarboxylate [21]; or magnesium isoglycyrrhizinate (MgIG), the magnesium salt of 18β-glycyrrhizic acid extracted from liquorice (a traditional Chinese medicine) [22], which have also been considered as a promising approach for further clinical development.

Due to the complexity and low prevalence of idiosyncratic DILI, undertaking randomised clinical trials (RCTs) faces multi-layered challenges. The aim of the current study was to perform a systematic review and meta-analysis to summarise the design and findings of RCTs in prevention and management of idiosyncratic DILI and non-acetaminophen DILI-related ALF.

2. Material and methods

2.1. Literature search and study selection

The protocol for the systematic review and meta-analysis was registered in the international prospective register of systematic reviews (PROSPERO) with the registration number CRD42020170475. This systematic review was performed following the PRISMA guidelines.

Eligible literature published up to January 31st, 2020 was identified through a search in PubMed, MEDLINE, EMBASE, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), and an additional search of grey literature (proceedings, white papers) in OpenGrey database to help minimise publication bias. The search strategy comprised the following terms and Boolean operators: "drug-induced liver injury" OR "drug-induced hepatotoxicity" OR "acute liver failure", combined with "preven*" OR "manag*" OR "treat*" OR "trial". Two researchers (HN and JSC) led the search, screened the titles and abstracts, and evaluated the adequacy of the studies. Any discrepancies were solved by consulting a senior researcher (MIL). References cited by the included studies and review articles and meta-analysis identified throughout the literature search were reviewed to retrieve additional studies.

2.2. Inclusion criteria

To be included, each study had to meet all of the following criteria: 1) be an original article; 2) be a RCT conducted in adult and/or paediatric population; 3) describe the use of pharmacological or herbal treatment on the prevention or management of idiosyncratic DILI or non-acetaminophen DILI-related ALF; 4) explain the methodology of the trial, including the inclusion criteria, treatment regimen in the experimental and control arm, and the definition and/or diagnosis of DILI and/or non-acetaminophen DILI-related ALF. Studies on animals or RCTs which used experimental treatment or extracorporeal approaches, i.e. neither pharmacological nor herbal drugs, and those which did not present stratified results for non-acetaminophen DILI-related ALF, were excluded. In case we could not retrieve the full text, corresponding authors were contacted and asked for a copy. If our request was not answered, the study was excluded.

2.3. Data extraction

Data were extracted by two researchers (HN and JSC), and discrepancies resolved through consultation to a third researcher (IAA). The following data were extracted from the included studies: surname of the first author, year of publication, RCT location, number of patients, treatment regimen in the experimental and control arm, primary and secondary outcomes, and diagnostic criteria of DILI. In those RCTs which provided a registry number, the protocol was consulted to retrieve further information. If any data were unclear, authors were contacted to obtain further information.

2.4. Quality assessment

The Review Manager (RevMan) software version 5.3 (the Cochrane Collaboration, 2014, Nordic Cochrane Center, Copenhagen, Denmark) was used to evaluate the quality of the included studies in terms of seven domains: random sequence generation, allocation concealment, blinding to participants and personnel, blinding to outcome assessment, incomplete outcome data, selective reporting, and other biases such as baseline imbalance, sample size estimation and use of intention-to-treat analysis (ITT) [23,24]. Each domain was judged according to the presence of high, low, or unclear/unknown risk of bias. Quality assessment was conducted by two researchers (HN and JSC), and disagreements were resolved by consulting a senior researcher (MIL).

2.5. Statistical analysis

Separate meta-analysis by outcome of interest (prevention or management of idiosyncratic DILI and non-acetaminophen DILI-related ALF) and drug were conducted if data were available. Additional subgroup analyses were performed on RCTs sharing certain methodological features (duration of treatment, blinding).

The effect size was calculated using random effects models and expressed by the pooled relative risk (RR) and the 95 % confidence interval (CI). Heterogeneity among studies was assessed with the I^2 statistic. This index ranges from 0 to 100 %, with higher values indicating greater heterogeneity [25]. Substantial heterogeneity was deemed if I^2 was over 50 % or p value <0.1. To further explore heterogeneity, the leave-one-out sensitivity analysis was conducted to test the influence of a single study on the overall effect size.

Publication bias was assessed using funnel plot techniques and Egger's regression test [26], as appropriate, given the limitations of these methods. A p value <0.1 was deemed as statistically significant. All analyses were carried out using STATA version 13 (Stata Corporation, College Station, TX, USA).

3. Results

3.1. Literature search

A total of 2,248 studies were retrieved on the database search. Of them, 1,298 were duplicate records. After screening the title and abstract, 924 records did not meet the inclusion criteria and were excluded, mainly irrelevant records to the current study or non-original articles, and 26 studies were reviewed. Of them, 14 records were not eligible and were excluded, mainly due to the lack of DILI criteria or relevant data, or non RCTs. After reviewing the references of the included studies and reviews and meta-analysis identified in the literature search, 10 additional studies were retrieved. Finally, 22 original RCTs were included (Fig. 1).

3.2. Study characteristics and quality assessment

Among 22 RCTs, 12 studies (n = 2,471 patients) were based on prevention and 10 studies in management (n = 797 patients) of DILI/non-acetaminophen DILI-related ALF. Main characteristics and methodologic quality assessment of each of the RCTs are summarised in Table 1 and Fig. 2.

Silymarin (eight studies), bicyclol (four), MgIG (three), NAC (three), tiopronin (one), L-carnitine (one), and traditional Chinese medicines

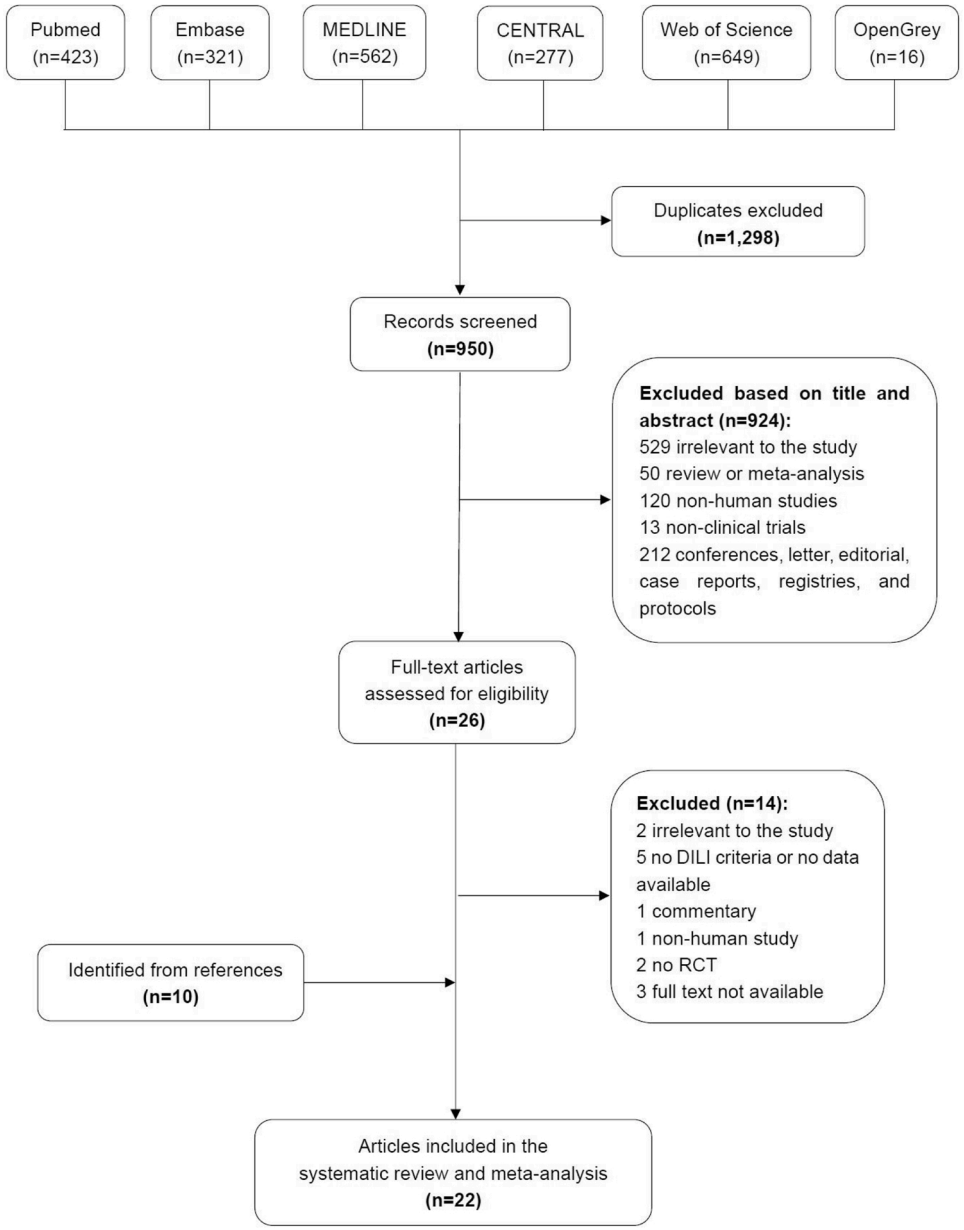

Fig. 1. Flow chart of the literature review process.

Table 1
Characteristics of randomised clinical trials included in the systematic review.

Study ID (location)	Mean age (SD)		Female (%)		Patients (N)[a]		Treatment regimen		Efficacy criteria	Duration (wk)	Diagnostic criteria	Withdraw (N)	Events (N)		Adverse events (N)	
	Exp	Con	Exp	Con	Exp	Con	Experimental	Control					Exp	Con	Exp	Con
Prevention of drug-induced liver injury																
Bicyclol																
Li 2014 (China) [27]	69	68	35	39	147	153	Chemotherapy, 25 mg bicyclol (t.d.s.)	Chemotherapy	Occurrence of grade I–IV liver injury	NA	CTCAE Version 3.0 [48]	6	25	72	NA	
Chu 2015 (China) [28]	18–65[b]		27	24	117	114	TBT, 200 mg GA (t.d.s.), 25 mg bicyclol (t.d.s.)	TBT, 200 mg GA (t.d.s.)	Incidence of mild to severe DILI	24	Diagnosis and treatment manual for adverse reactions of anti-TB drugs [49]	9	10	21	4	3
L-carnitine																
Hatamkhani 2014 (Iran) [29]	37 (15)	29 (15)	24	26	54	62	TBT, 1,000 mg L-carnitine (b.d.)	TBT, placebo (b.d.)	Occurrence of anti-TB drug hepatotoxicity	4	ALT or AST >3xULN (with symptoms) ALT or AST >5xULN (without symptoms) RUCAM	27	9	20	0	0
Magnesium isoglycyrrhizinate																
Yan 2015 (China) [30]	60 (10)	60 (10)	47	47	114	102	Chemotherapy, 0.2 g MgIG into 250 mL 10% GLC (o.d.)	Chemotherapy, 1.2 g GSH into 250 mL 5% GLC (o.d.)	DILI incidence	1	WHO Adverse Drug Reaction Terminology [50]	0	6	12	NA	
N-acetylcysteine																
Baniasadi 2010 (Iran) [31]	75 (8)	73 (7)	50	47	28	32	TBT, 600 mg NAC (b.d.)	TBT	Anti-TB DILI incidence	2	ALT and/or AST >5xULN. TBil >1.5 mg/dl Elevated levels of ALT and/or AST with symptoms	0	0	12	NA	
Silymarin																
Gu 2015 (China) [32]	37 (14)	36 (14)	35	33	277	291	TBT, 70 mg silymarin (t.d.s.)	TBT	DILI incidence	8	Diagnosis and treatment manual for adverse reactions of anti-TB drugs [49]	0	21	31	5	3
Luangchosiri 2015 (Thailand) [33]	56[c] (15–78)	52[c] (21–83)	63	57	27	28	TBT, 140 mg silymarin (t.d.s.)	TBT, placebo (t.d.s.)	Adverse events rate Maximum ALT level within 4 weeks after treatment	4	ALT >2xULN, TBil >1.5 mg/dl, increase in ALT and jaundice, no other explanations of elevation of liver enzymes, and normalisation after withdrawal	3	1	9	3	3
Marjani 2016 (Iran) [34]	50	50	46	49	35	35	TBT, 140 mg silymarin (t.d.s.)	TBT, 140 mg placebo (t.d.s.)	Anti-TB DILI incidence DILI incidence Adverse events rate	2	ALT or AST >3xULN with symptoms ALT or AST >5xULN, or TBil >2 mg/dl	2	6	3	14	14
Zhang 2016 (China) [35]	>12[d]		30	23	183	187	TBT, 200 mg silymarin (b.d.)	TBT, vitamin C tablet	Probable and possible DILI Peak AST/ALT ratio Maximum altered ALP or GGT value Adverse events rate	8	Probable DILI: ALT or AST >3xULN and TBil >2xULN	9	1	0	69	65

(*continued on next page*)

Table 1 (*continued*)

Study ID (location)	Mean age (SD)		Female (%)		Patients (N)[a]		Treatment regimen		Efficacy criteria	Duration (wk)	Diagnostic criteria	Withdraw (N)	Events (N)		Adverse events (N)	
	Exp	Con	Exp	Con	Exp	Con	Experimental	Control					Exp	Con	Exp	Con
Heo 2017 (South Korea) [36]	58 (14)	59 (15)	38	31	45	58	TBT, 140 mg silymarin (b.d.)	TBT, placebo (b.d.)	DILI incidence	8	AST or ALT >3xULN or TBil >2xULN	18	6	10	NA	
Wu 2017 (China) [37]	48 (16)	45 (16)	41	41	118	114	TBT, 70 mg silymarin (t.d.s.)	TBT	DILI incidence	8	Guidelines for the management of drug-induced liver injury [51]	4	3	16	7	9
									Incidence according to sex and age groups							
									Adverse events rate							
Tiopronin																
Li 2014 (China) [38]	54 (2)	52 (2)	47	47	86	64	Chemotherapy, 200 mg TP (o.d.), 2 days each 2 wk	Chemotherapy	Incidence of chemotherapy-induced hepatoxicity	NA	CTCAE Version 3.0 [48]	30	7[f]	18[f]	NA	
									Chemotherapy delays or dose reductions and transaminase elevations							
Management of drug-induced liver injury																
Bicyclol																
Tang 2013 (China) [39]	40 (6)	39 (6)	39	42	26	26	TBT, 50 mg bicyclol (t.d.s.)	TBT, 100 mg DG (t.d.s.)	Normalisation or improvement of liver biochemical parameters	2	ALT >2xULN and normal TBil	0	18	12	NA	
Wu 2017 (China) [40]	24–66[b]		20	19	79	78	25 mg bicyclol (t.d.s.)	456 mg PPC (t.d.s.)	Decrease of serum ALT levels	4	RUCAM ≥6	11	45	31	2	2
									Normalisation rate of serum ALT at 2 and 4 wk		ALT 2–5xULN and TBil ≤2xULN, liver biochemical abnormalities <3 months					
									Comprehensive efficacy at 4 wk							
Magnesium isoglycyrrhizinate																
Tang 2012 (China) [41]	34 (14)	34 (16)	43	45	35	20	200 mg MgIG (o.d.)	200 mg TP (o.d.)	Normalisation or improvement of liver biochemical parameters	2	DDW-J >6	0	23[g]	8[g]	12	3
									Adverse events rate		ALT, AST, TBil, or ALP ≥2xULN and TBil ≤3xULN, liver biochemical abnormalities <3 months					
Wang 2019 (China) [42]	40 (15) 36 (15)	34 (12)	34	27	59	59	250 mL 5% GLC, 100 mg MgIG, 200 mg simulated TP (o.d.).	250 mL 5% GLC, 200 mg simulated MgIG, 200 mg of TP (o.d.)	Rate of ALT normalisation at wk 4	4	RUCAM ≥6	19	50	36	11	18
			38		56		250 mL 5% GLC, 200 mg MgIG, 200 mg simulated TP (o.d.)		Rate of ALT and AST normalisation		ALT ≥2xULN and TBil ≤3xULN, liver biochemical abnormalities <3 months		48		13	
									Changes of ALT and AST at wk 1, 2, 3 and 4							
Silymarin																
	53[e] (42)	47[e] (41)	39	38	29	26	5 mg/kg silymarin (o.d.)	1 mg FA (o.d.)	Decrease/normalisation of liver enzymes	4	ALT and/or AST >3xULN and ALP > 2xULN	5	ALT: 1	ALT: 8	0	0

(*continued on next page*)

Table 1 (*continued*)

Study ID (location)	Mean age (SD)		Female (%)		Patients (N)[a]		Treatment regimen		Efficacy criteria	Duration (wk)	Diagnostic criteria	Withdraw (N)	Events (N)		Adverse events (N)	
	Exp	Con	Exp	Con	Exp	Con	Experimental	Control					Exp	Con	Exp	Con
Asgarshirazi 2017 (Iran) [43]									Decreasing trend and rebound elevation of enzymes after cessation of the treatment				AST: 0	AST: 11		
Marjani 2019 (Iran) [44]	52 (4)	57 (4)	52	56	27	27	TBT, 140 mg silymarin (t.d.s.)	TBT, placebo	Time of normalisation of liver enzymes and TBil Severity, duration, mortality, and hospital stay Adverse events rate	2	ALT or AST >3xULN (with hepatotoxicity symptoms) AST or ALT >5x ULN or TBil >2 mg/dl	1	ALP: 2 9 ± 1[h]	ALP: 2 8 ± 2[h]	3	4
Traditional Chinese Medicines																
Zhou 2018 (China) [45]	42 (4)	42 (5)	42	46	50	50	400 mg TP added into 5% GLC solution (o.d.) and 10 mL Yinzhihuang (t.d.s.)	400 mg TP added into 5% GLC solution (o.d.)	Normalisation or improvement of liver biochemical parameters Adverse events rate	4	Guidelines for the management of drug-induced liver injury [51]	0	28	20	6	14
Yuan 2019 (China) [46]	34 (7)	34 (7)	56	51	45	45	100 mL Xuebijing added into 100 mL saline, and 150 mg MgIG added into 250 mL 5% GLC solution (o.d.)	150 mg MgIG added into 250 mL 5% GLC solution (o.d.)	Normalisation or improvement of liver biochemical parameters Time to normalisation Adverse events rate	2	TBil, ALP, AST, or ALT ≥2xULN, duration of abnormal liver function 2−12 wk.	0	23	17	0	0
Management of DILI-related acute liver failure																
N-acetylcysteine																
Lee 2009 (USA) [12]	NA		NA		19	26	5% dextrose with NAC (150 mg/kg/h over 1 h, 12.5 mg/kg/h for 4 h, 6.25 mg/kg/h for 67 h)	5% dextrose	Overall survival rate at 3 wk Transplant-free survival, transplantation rate at 3 wk	72 h	INR ≥1.5 due to an illness of <24 wk duration	NA	15	17	NA	
Nabi 2017 (India) [47]	NA		NA		10	5	NAC (150 mg/kg over 1 h, 12.5 mg/kg/h for 4 h, 6.25 mg/kg/h for 67 h)	5% dextrose infusion (placebo) for 72 h	Overall survival rate Safety and duration of hospital stay	72 h	INR ≥1.5, any degree of encephalopathy caused by illness of duration <8 wk	0	10	3	0	NA

Exp: experimental group; Con: control group; NA: not available; wk: weeks; MgIG: Magnesium isoglycyrrhizinate; NAC: *N*-acetylcysteine; TBT: standard anti-tuberculosis treatment; GSH: glutathione; TP: tiopronin; FA: folic acid; DG: diammonium glycyrrhizinate; PPC: polyene phosphatidylcholine; GA: glucurolactone; GLC: glucose; DILI: drug-induced liver injury; ULN: upper limit of normality; INR: International normalized ratio; TB: tuberculosis; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; TBil: total bilirubin; o.d.: once daily; b.d.: twice daily: t.d.s.: three times a day; CTCAE: Common Terminology Criteria for Adverse Events; DDW-J: Digestive Disease Week-Japan; RUCAM: Roussel Uclaf Causality Assessment Method.
CTCAE version 3.0: ALT, AST or ALP > 2.5xULN or TBil >1.5xULN.
Diagnosis and treatment manual for adverse reactions of anti-tuberculosis drugs: ALT >2xULN and/or TBil >2xULN.

WHO Adverse Drug Reaction Terminology: ALT, AST, ALP or TBil >1.25xULN.
Guidelines for the management of drug-induced liver injury: ALT ≥5xULN; ALP≥2xULN, especially in patients with elevated 5′-nucleotidase or GGT, and without bone-diseases-related ALP elevation; ALT ≥3xULN and TBil ≥2xULN.
[a] Patients included in the final analysis.
[b] Age range.
[c] Median and interquartile range.
[d] Inclusion age.
[e] Age in months.
[f] Number of patients with elevated ALT levels.
[g] Number of patients with normal ALT levels.
[h] Time to normalisation (days).

Yinzhihuang (one) and Xuebijing (one) were tested in the intervention arm, while control arm mostly received either the standard supportive care (chemotherapy or anti-tuberculosis [anti-TB] treatment regimen [a combination of isoniazid, rifampicin, pyrazinamide, and ethambutol], when required), or placebo. Of note, Wang et al. [42] conducted a phase II trial exploring two different doses of the experimental compound MgIG. Both experimental groups treated with MgIG were included separately in our analysis.

Most of the RCTs [27–47] were conducted in Asian countries (59 % in China), except for one trial of non-acetaminophen ALF conducted in the United States [12]. Heterogeneity was observed due to variations in the DILI/ALF case definitions and inclusion/exclusion criteria. Most studies defined DILI on a range of liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) or total bilirubin (TBil) elevations from 1.25 to 5-fold upper limit of normality (ULN). Two studies [37,45] defined DILI using the criteria of Aithal et al. [52] referred in the Chinese Guidelines for the management of drug-induced liver injury [51], two studies [27,38] used the definition in the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 [48], another two trials [28,32] used the definition in the Chinese Diagnosis and treatment manual for adverse reactions of anti-tuberculosis drugs [49], and another trial [30] used the World Health Organization (WHO) Adverse Drug Reaction Terminology [50]. Non-acetaminophen ALF was consistently defined as international normalized ratio (INR) ≥1.5 and any degree of encephalopathy and coagulopathy. The use of liver-specific causality assessment scales was limited to four RCTs: Roussel Uclaf Causality Assessment Method (RUCAM) in three studies [29,40,42] and Digestive Disease Week-Japan (DDW-J) in one study [41]. Most studies included only adult population (≥18 years), including two studies with patients older than 60 years [27, 31], whilst one study included only population aged less than 18 years [43], and other study included population aged >12 years [35]. Main efficacy criteria in the prevention RCTs was DILI incidence [27–32,34, 36–38], maximum ALT, ALP or GGT level [33,35], or peak of AST/ALT ratio [35], and in management RCTs the 50 % decrease or normalisation of the liver parameters, or survival rate in DILI-related ALF patients. Duration of treatment ranged from 72 h to at least eight weeks. In addition, 15 trials reported adverse events (Table 1).

A total of 15 (68 %) studies reported an appropriate randomisation method, mainly random number table [27,28,35,37,38,40,43,46] and block randomisation [12,29,33,34,36,45]. Only two trials [33,43] described opaque envelope as the allocation concealment method. Eight (36 %) RCTs were double-blind [12,29,33,34,36,41,42,44] and four were open-label studies [31,32,35,43], sample size estimation was done in nine (41 %) RCTs [12,29,31,33–35,41,43,44]. A total of four (18 %) RCTs involving 377 patients used an ITT approach to analyse their data [12,33,36,42]. In 13 studies, withdrawals during follow-up were reported. Remarkably, only one study, Luangchosiri et al. [33] presented a low risk of bias in all quality domains evaluated (Fig. 3).

Severity of DILI was assessed in five RCTs [28,30,32,33,37]. Two trials [28,32] used the Diagnosis and treatment manual for adverse reactions of anti-TB drugs [49], two trials [30,33] used the WHO Adverse Drug Reaction Terminology [50], and one trial [37] used the Chinese Guidelines for the management of DILI [51]. Only one management study [42] presented the odds of ALT normalisation according to the type of liver injury (hepatocellular, cholestatic and mixed).

Interestingly, only four of the products tested in the RCTs included were authorised in the European Union, either centrally or nationally authorised: silymarin for treating toxic liver damage due to medicines, L-carnitine for preventing valproic acid hepatotoxicity, NAC for treating paracetamol overdoses, and tiopronin is only authorised for renal diseases (cystinuria). Bicyclol, MgIG, and the traditional Chinese medicines Yinzhihuang and Xuebijing were authorised in China. (Table 2).

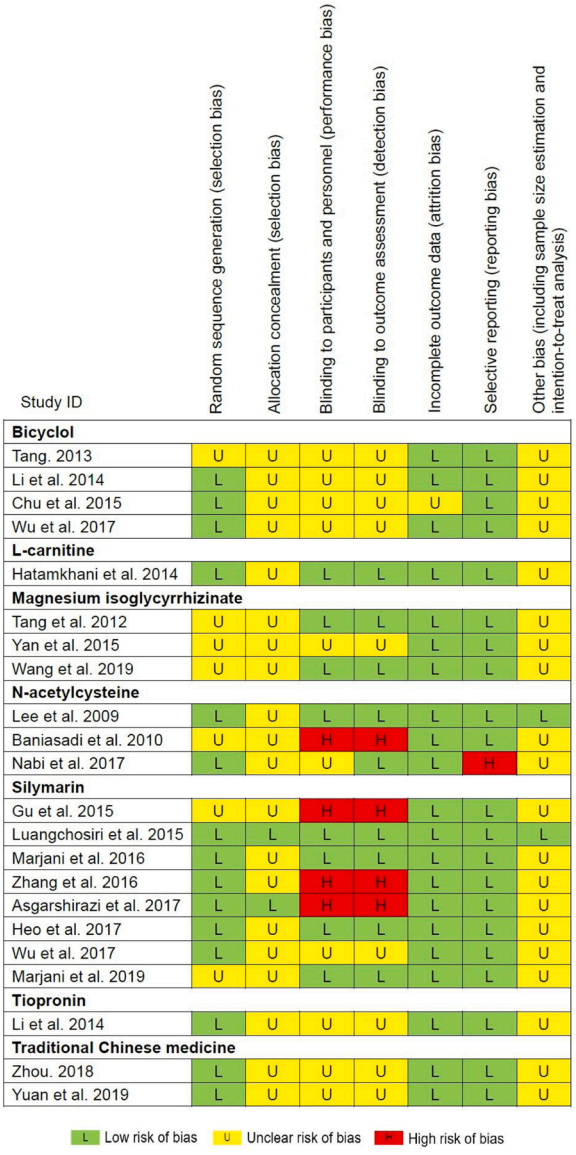

Fig. 2. Individual risk of bias assessment of included randomised clinical trials.

3.3. Silymarin

Six RCTs evaluated the efficacy of silymarin in the prevention of DILI [32–37]. No differences in patients who received silymarin compared to those in the control arm were found (RR = 0.60; 95 % CI 0.29–1.27). However, significant heterogeneity between studies was detected (I^2 = 56.4 %; p = 0.043) (Fig. 4). Findings from sensitivity analyses did not differ substantially.

A subgroup analysis by weeks of treatment was conducted. Patients treated with silymarin for four weeks showed a significant reduction of DILI incidence in patients treated with anti-TB drugs (RR = 0.29; 95 % CI 0.09−0.92). However, no reduced incidence was found in patients treated neither two nor eight weeks (RR = 0.89; 95 % CI 0.45–1.74, and RR = 0.89; 95 % CI 0.42–1.90, respectively). No significant heterogeneity was found in any of the subgroups even though DILI definition differed among the studies. (Supplemental Fig. 1).

Silymarin was not effective in preventing DILI in open-/unclear blind trials (n = 1,170; RR = 0.51; 95 % CI 0.15–1.69) nor double-blind RCTs (n = 228; RR = 0.68; 95 % CI 0.18–2.57). Both groups showed significant heterogeneity (I^2 = 62.0 %; p = 0.072, and I^2 = 65.4 %; p = 0.056, respectively), and results from sensitivity analyses did not vary significantly.

An ancillary analysis of severity of liver injury was conducted. Patients treated with silymarin did not show a reduced risk of mild (RR = 0.49; 95 % CI 0.22–1.08) nor moderate liver injury (RR = 0.49; 95 % CI 0.12–1.93). Notably, silymarin administration was effective in preventing the development of severe liver injury (RR = 0.11; 95 % CI 0.01−0.90). No heterogeneity was found in any subgroup.

Two RCTs assessed the efficacy of silymarin on the management of DILI. Marjani et al. [44] in a double-blind, placebo-controlled trial, of 54 adult patients under anti-TB treatment who developed DILI did not find any effect of silymarin in reducing duration and severity of DILI or duration of hospitalisation. In addition, Asgarshizari et al. [43] conducted an open-label trial including 55 children under antiepileptic treatment who had experienced DILI. Of them, 29 were treated with 5 mg/kg of silymarin and 26 were treated with 1 mg of folic acid. Although both treatments were associated with a significant decrease of liver enzymes at the end of the study, a higher percentage of children who received folic acid showed normal ALT, AST and GGT values compared to children treated with silymarin. Unfortunately, due to the differences in outcome measures, findings from these two trials could not be combined in a quantitative analysis.

3.4. Bicyclol

Two RCTs tested the efficacy of bicyclol in preventing the onset of DILI in patients receiving chemotherapy [27] or anti-TB treatment [28]. Patients who received bicyclol showed a significant reduction in the risk of developing DILI compared to those allocated in the control arm (RR = 0.38; 95 % CI 0.27−0.54), with no heterogeneity across studies (I^2 = 0%; p = 0.545) (Fig. 4).

Two trials evaluated the efficacy of bicyclol on the management of DILI. Altogether, patients with liver injury who were treated with bicyclol showed higher normalisation rates compared to those allocated in the standard supportive care arm (either diammonium glycyrrhizinate [39] or polyene phosphatidylcholine [40]) (RR = 0.69; 95 % CI 0.52−0.91), with no heterogeneity between studies (I^2 = 0%; p = 0.556) (Fig. 5).

3.5. Magnesium isoglycyrrhizinate

One trial [30] tested the preventive effect of MgIG compared to glutathione in 216 adult patients receiving chemotherapy treatment. The incidence of hepatotoxicity grade I according to the WHO Adverse Drug Reaction Terminology [50] after one week of chemotherapy treatment was found significantly lower in patients who were treated with MgIG compared to those who received glutathione (5.3 % against 11.8 %, respectively; p < 0.01). Indeed, differences in liver enzymes were significantly lower in patients allocated to the experimental arm compared to those in the control arm.

Two double-blind RCTs assessed the role of MgIG in the management of DILI [41,42]. Patients who had DILI and were treated with MgIG showed significantly greater ALT normalisation rates compared to those allocated in the control group who received tiopronin (RR = 0.40, 95 % CI 0.27−0.60), with no heterogeneity across studies (I^2 = 0%; p = 0.925) (Fig. 5).

3.6. N-Acetylcysteine

In an open-label trial conducted in 60 patients aged 60 and over, Baniasadi et al. [31] studied the efficacy of NAC on the prevention of anti-TB DILI. Among 28 patients who received standard anti-TB treatment combined with 600 mg of NAC, none of them developed DILI after two weeks of follow-up. In contrast, among 32 patients who only received standard anti-TB treatment, 12 of them (37.5 %) experienced DILI within two weeks of follow-up.

On the other hand, two RCTs assessed the role of NAC in survival of

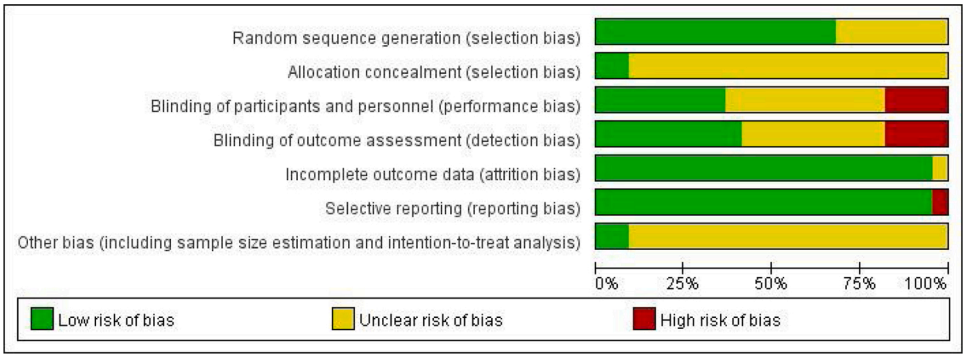

Fig. 3. Risk of bias presented as percentages across the included randomised clinical trials.

Table 2
Summary of product characteristics of agents used in clinical trials in DILI and authorisation status within the European Union countries.

ATC	Product	Presumed mechanism of action	Centralised authorisation (yes/no)	National authorisation (yes/no)	Labelled indications	Authorised pharmaceutical forms
A05B	Silymarin (*Silybum marianum (L.) Gaertn.*, *fructus*)	Antioxidative, antifibrotic, anti-inflammatory, protein synthesis stimulating and membrane protecting mechanisms	Yes	NA	Toxic liver damage, e.g. due to alcohol, medicines, or due to metabolic dysfunctions like diabetes; supportive treatment of chronic inflammatory liver diseases and cirrhosis of the liver	Capsules or tablets
NA	Bicyclol[b]	Effect of scavenging free radicals and protecting liver cell membranes; protection of liver cell nuclear DNA from damage and reduction of the occurrence of cell apoptosis	No	No	Treatment of elevated aminotransferase caused by chronic hepatitis	Tablets
A16AA01	L-carnitine[a]	Favor the metabolic flow in the Krebs cycle, with the same mechanism with which stimulates the activity of pyruvate dehydrogenase and, in skeletal muscle, the oxidation of branched fatty acids	No	Yes	Treatment of primary and secondary L-carnitine deficiencies; treatment of hyperammonemic encephalopathy and/or hepatotoxicity due to valproic acid overdose/toxicity; prophylactic treatment in patients receiving valproic acid who are at increased risk of hepatotoxicity; treatment of secondary L-carnitine deficiency in patients undergoing long-term hemodialysis	Injection
NA	Magnesium isoglycyrrhizinate[b]	Prevention of the increase of serum transaminase, reduction of hepatocyte degeneration, necrosis, and inflammatory cell infiltration	No	No	Chronic viral hepatitis and acute drug-induced liver injury	Injection
R05CB01	*N*-acetylcysteine[a]	Cytoprotective activity in the respiratory system against damaging action of oxidative stress by oxidative free radicals	No	Yes	Adjunctive treatment in respiratory processes that occur with excessive or thick mucous hypersecretion; treatment of paracetamol overdoses	Tablets or injection
G04BX16	Tiopronin[c]	Reduction of soluble cystine by the formation of a water-soluble mixed disulfide as a result of a thiol-disulfide exchange with cystine	No	Yes	Prevention of cystine stone formation in adults and pediatric patients 20 kg and greater with severe homozygous cystinuria	Tablets
NA	Xuebijing[b]	NA	No	No	Removal of blood stasis and detoxification; fever, wheezing, palpitations, irritability, and other syndromes of blood stasis and poison; treatment of systemic inflammatory response syndrome induced by infection	Injection
NA	Yinzhihuang[b]	NA	No	No	Acute, persistent, chronic hepatitis and severe hepatitis (type I) caused by damp-heat toxins, and other types of severe hepatitis	Oral liquid

[a] Information retrieved from the Spanish Medicines Agency.
[b] Drug authorised in China. Information retrieved from the summary of product characteristics.
[c] Information retrieved from the French Medicines Agency.

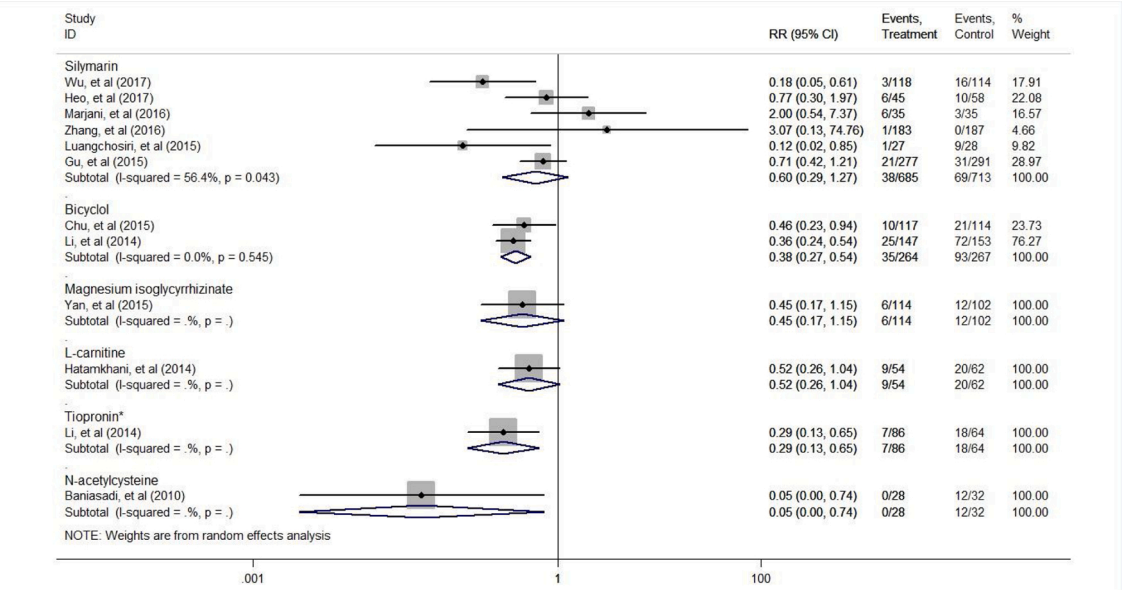

Fig. 4. Pooled efficacy of pharmacological/herbal agents in randomised clinical trials in drug-induced liver injury prevention.
* Efficacy is measured as preventing elevated ALT levels.

adult patients with idiosyncratic drug-induced ALF [12,47]. The use of NAC in these patients (n = 60) did not show improvements in overall survival rates (RR = 0.44; 95 % CI 0.11–1.68), with low heterogeneity across studies (I^2 = 20.4 %; p = 0.262) (Fig. 5).

3.7. Tiopronin

Li and colleagues [38] performed a trial to evaluate the efficacy of tiopronin in chemotherapy-induced hepatotoxicity. They reported a significant lower incidence of chemotherapy-induced liver injury in 86 patients whose treatment was supplemented with 200 mg of tiopronin (abnormal [>2.5xULN] ALT, AST and TBil rates were 8.3 %, 7.8 % and 6.7 %, respectively) compared to 64 patients who received standard chemotherapy treatment alone, with frequencies of abnormal ALT, AST and TBil values of 29 %, 26 % and 31 %, respectively (RR = 0.29; 95 % CI 0.13−0.65) (Fig. 4).

3.8. L-Carnitine

An Iranian double-blind trial [29] aimed to evaluate the efficacy of oral L-carnitine in preventing anti-TB DILI. After four weeks of treatment, among 54 patients who received standard anti-TB treatment supplemented with 2,000 mg of oral carnitine solution daily, nine patients (17 %) developed DILI, while 20 of 62 patients (32 %) who only received standard anti-TB treatment experienced DILI (p = 0.049).

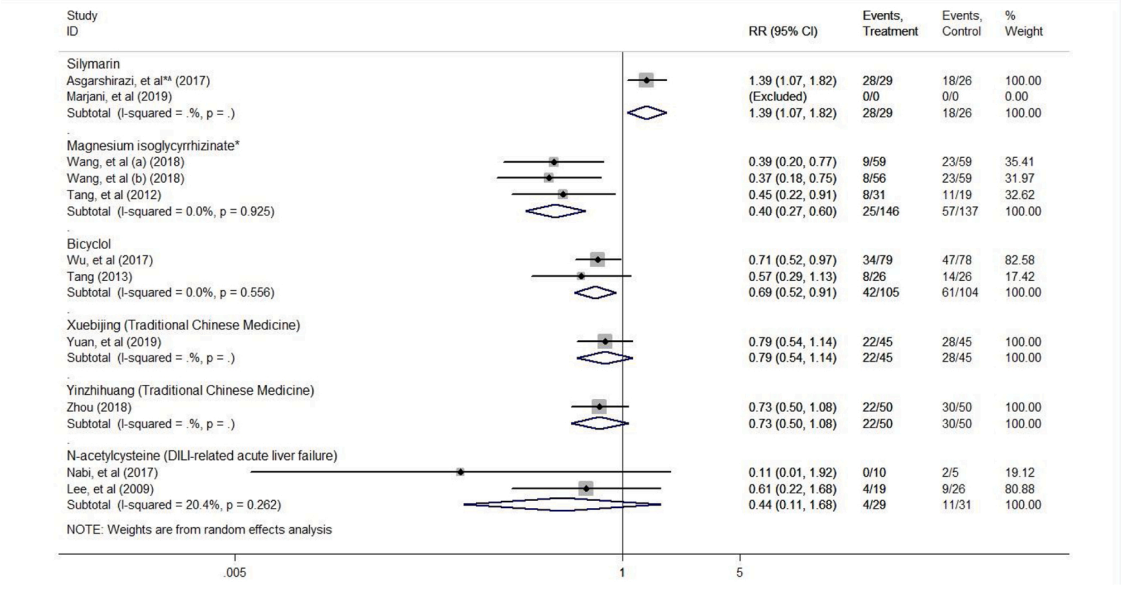

Fig. 5. Pooled efficacy of pharmacological/herbal agents in randomised clinical trials in drug-induced liver injury management.
* Efficacy is measured as ALT normalisation; ^ Paediatric population.
(a) 100 mg per day of magnesium isoglycyrrhizinate; (b) 200 mg per day of magnesium isoglycyrrhizinate.
Marjani et al. [44] used as efficacy criteria the time of normalisation of liver enzymes.

3.9. Traditional Chinese medicines

Two trials reported the efficacy of traditional Chinese medicines combined with other drugs in the treatment of DILI. Zhou [45] reported that among 50 patients with DILI (defined according to Aithal et al. [52]) who were treated with tiopronin combined with Yinzhihuang (composed of *Herba artemisiae scopariae* [Yin Chen], *Gardenia* [Zhi Zi], honeysuckle [Jin Yin Hua], and *Scutellaria* [Huang Qin]), in 46 of them (92 %) liver parameters tended to normalisation, compared to 36 (72 %) who received only tiopronin ($p < 0.05$). Moreover, Yuan et al. [46] reported that 45 DILI cases (defined as ALT, AST, ALP or TBil ≥2xULN) who received a combined treatment of MgIG and Xuebijing (composed of *Angelica sinensis* [Dang Gui], *Salvia miltiorrhiza* [Dan Shen], *Ligusticum chuanxiong* [Chuan Xiong], Radix Paeoniae Rubra [Chi Shao], and safflower [Hong Hua]) showed higher liver indices improvement or normalisation rates (39 patients, 87 %) compared to 31 out of 45 cases (69 %) who were treated only with MgIG ($p < 0.05$). However, neither Yinzhihuang (RR = 0.73; 95 % CI 0.50–1.08) nor Xuebijing administration (RR = 0.79; 95 % CI 0.54–1.14) was effective when the outcome was restricted to normalisation of liver parameters (Fig. 5).

3.10. Adverse effects

An analysis to study the adverse effects rate of drugs used in the prevention and management of DILI was performed. The most frequent reported adverse reactions of silymarin were nausea, anorexia, and abdominal pain. The reported adverse reactions of bicyclol comprised dizziness, headache, abdominal distension, and mild diarrhoea. The main adverse reactions associated to MgIG were granulocytopenia, fever and nausea. Adverse effects related to NAC treatment were nausea and vomiting. Of note, eight studies (bicyclol [two], MgIG [one], NAC [three], silymarin [one], tiopronin [one]) did not provide complete information of adverse events (Table 1).

Patients who were treated with silymarin for either preventing or treating DILI, compared to those who received placebo or standard supportive care, did not show a higher risk of adverse events (RR = 1.05; 95 % CI 0.84–1.32). Likewise, neither patients who received bicyclol (RR = 1.17, 95 % CI 0.36–3.79) nor MgIG (RR = 0.88; 95 % CI 0.47–1.63) were at increased risk for presenting adverse events. No substantial heterogeneity was detected. Therefore, these drugs showed a safe profile (Fig. 6).

3.11. Publication bias

Despite the few number of studies available, no publication bias was (cautiously) suggested on regard of RCTs which used silymarin on the prevention of DILI ($p = 0.825$), nor those trials which assessed the efficacy of MgIG on the management of DILI ($p = 0.991$) (Supplemental Fig. 2). Unfortunately, publication bias could not be evaluated for the remaining pharmacological or herbal agents due to the low number of studies available.

4. Discussion

In recent years, prevention and management of DILI have received growing attention due to its increasing public health burden [2]. To our knowledge, this is the first systematic review that summarises the findings of RCTs aimed to prevent idiosyncratic DILI and manage the development of ALF in DILI. This review emphasises the lack of standardised diagnostic criteria of DILI, as well as differences in design and methodology of the RCTs analysed.

Several agents with presumed beneficial effects on DILI have been tested in RCTs in the past years, especially in Eastern countries, probably due to the higher prevalence of DILI caused by anti-TB agents compared to Western countries [53]. Silymarin has been the most commonly evaluated agent in clinical trials. Several mechanisms underlying the hepatoprotective effect of silymarin have been described, including its antioxidant activity in the liver and its inhibitor role of several isoforms of hepatic cytochrome P450 2E1 induced by anti-TB drugs [54,55]. In addition, a recent review concluded that silymarin was a well-tolerated agent that can be used as a supportive treatment in most forms of liver disease [56].

Our analysis showed no overall apparent beneficial effect of silymarin on DILI prevention. When stratified analyses by treatment duration were performed, silymarin exerted a hepatoprotective effect on anti-TB DILI incidence only when patients were treated for four weeks. Though prior studies demonstrated that the development of clinical symptoms in anti-TB hepatotoxicity had a wide time span, ranging from six weeks to six months [57], other authors reported that nearly 70 % of patients developed anti-TB hepatotoxicity within 30 days, and 88 % within eight weeks [58,59]. Nonetheless, the results of this post hoc analysis should be interpreted carefully to avoid misleading conclusions. Due to the variability in the trial duration and availability of data, each subgroup included different trials. Consequently, the capability to detect estimated effects varied, and may explain these findings. Interestingly, in a recent meta-analysis of silymarin RCTs stratified to treatment duration, the authors also faced the same methodological shortcoming [60].

Nevertheless, as reported in prior systematic reviews, findings from low methodological quality trials (open-/unclear blinded) tended to exaggerate the benefits of silymarin treatment when compared to double-blind trials [61].

The Chinese Society of Hepatology Guidelines suggests that silymarin may be used to treat mild liver inflammation [62]. However, only three RCTs reported DILI according to its severity, and two of them were open-/unclear blinded trials, which may limit the validity of these findings. Nonetheless, findings reported by Luangchoshiri et al. [33] in a high-quality trial are in line with Chinese Society of Hepatology Guidelines, although the small sample size would have limited the statistical power of their analyses.

In addition, DILI patients treated with silymarin did not show clinical improvements in the two management RCTs analysed [43,44]. Nonetheless, the low number of patients should be taken into account as a limitation that may have underpowered the analysis, which precludes to detect differences between the groups of treatment.

Previous investigations have reported a hepatoprotective effect of bicyclol on DILI in mice, treated with up to 200 mg/kg of the compound, mediated by its antioxidant and anti-inflammatory properties [63–66]. However, evidence for the efficacy in the treatment of DILI in humans is still scarce. In a Chinese pharmacoeconomic study using a decision tree analysis approach to evaluate four hepatoprotective drugs (bicyclol, tiopronin, reduced glutathione and diammonium glycyrrhizinate) for the treatment of DILI, authors concluded that bicyclol showed the greatest efficacy and safety, as well as the lower incremental cost-effectiveness ratio [67]. However, the fact that all trials were conducted in China do not permit generalisability of these findings.

The analysis of four trials in the current study showed that administration of bicyclol was related to a reduced incidence of DILI and higher normalisation rates. It should be noted that the two trials assessing the role of bicyclol in DILI prevention diverged in the DILI definition and the eligible population. Indeed, the threshold in aminotransferases >2.5xULN to define DILI are lower to those recommended in Clinical Practice Guidelines [2,62,68], and may be misleading. Further, one of these trials [28] evaluated the efficacy of bicyclol in conjunction with glucurolactone, used in prevention of anti-TB DILI in China, compared to the control group who received glucurolactone, which may have distorted the findings. In addition, there were differences regarding the DILI criteria, doses administered and the control group in the two DILI management trials. Given the low number of trials, the lack of information about its methodological design (i.e. allocation concealment and blinding), and the aforementioned limitations, findings should be interpreted cautiously.

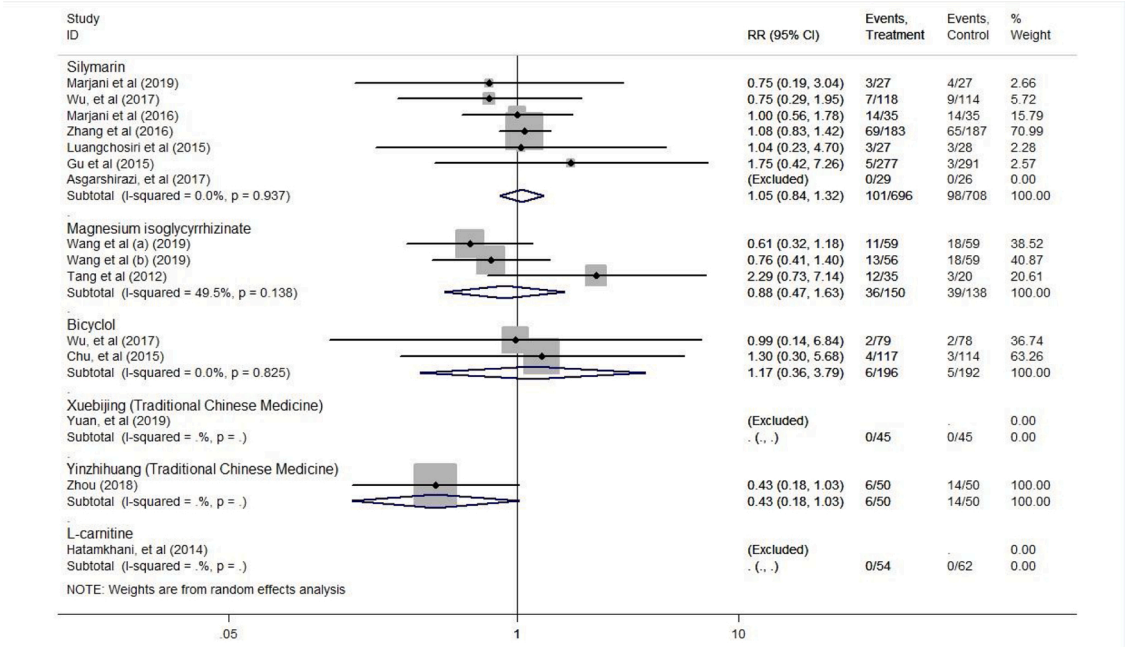

Fig. 6. Pooled effects of adverse events of pharmacological/herbal agents tested in randomised clinical trials in drug-induced liver injury prevention/management. Eight trials did not provide complete information of adverse events.
(a) 100 mg per day of magnesium isoglycyrrhizinate; (b) 200 mg per day of magnesium isoglycyrrhizinate.

MgIG is used in China as an anti-inflammatory and hepatoprotective agent in the treatment of inflammatory liver diseases [22,69]. Though the exact mechanisms in human remain to be elucidated, some studies in animal models have proposed that 9–50 mg/kg of MgIG hepatoprotective effects may be correlated with an attenuation of oxidative stress [70,71]. Despite an apparent reduced incidence of DILI and greater ALT normalisation rates in patients treated with parenteral MgIG, our findings were based on three trials with poor description of methodological design, low stringent DILI diagnostic criteria, short-term follow-up, and lack of clinically meaningful endpoints. Therefore, the validity of these results is compromised and should be interpreted cautiously.

Despite there being no specific treatment for DILI-related ALF, with the exception of liver transplantation, NAC has been tried in idiosyncratic drug-related ALF given its efficacy and good safety profile in acetaminophen-induced ALF. Hu et al. [72] in a meta-analysis of clinical studies, concluded that NAC treatment improved transplant-free survival and survival after transplantation, but not overall survival in patients with non-acetaminophen-induced ALF. Although case reports have supported the use of NAC in drug-induced ALF [73], findings from a systematic review were inconclusive due to the low available evidence [74]. In the present study, restricting the study population to idiosyncratic drug-induced ALF patients, no improvements in overall survival in patients treated with NAC were found. It should be noted that, based on the limited number of trials and the lack of data of drug-induced ALF patients in RCTs, these findings may be underpowered. Since drugs are a main cause of ALF [1,75], and NAC is the most cogent drug in treating acetaminophen overdose, there is a need of high quality RCTs to validate the efficacy of NAC in preventing and treating non-acetaminophen DILI-related ALF.

Although corticosteroids have been suggested in the management of some forms of DILI, no RCTs using these agents were identified. Noticeably, a recent systematic review focused on the management of immune-mediated hepatotoxicity pointed out the possibility of avoiding corticosteroids treatment in patients with immune-related hepatitis due to immune checkpoints inhibitors [76]. Therefore, to what extent the use of corticosteroids in the management of DILI would be useful remain to be elucidated.

The need of high-quality clinical trials to enhance the prevention and management of DILI has been underscored in the past years [77]. Several differences in trial design were identified across the RCTs included. Prior investigations on the influence of study design characteristics on intervention effects concluded that bias derived from an inadequate or unclear sequence generation or allocation concealment, and the lack of a double-blind design, may exaggerate the estimates of intervention effects, especially in trials which assessed subjective outcomes [78,79]. Although the outcomes measured in the included RCTs were evaluated objectively (based on established laboratory parameters), the small sample sizes limited the number of robust endpoints such as ALF, transplantation, or death. Therefore, effects are likely to be over-estimated due to selection bias.

Another critical concern identified throughout this systematic review is the heterogeneity in DILI case qualification. DILI criteria ranged from a 1.25-fold elevation the ULN of liver biochemistries to a threshold of 5 times the ULN. This lack of harmonisation in criteria makes the comparison between studies extremely difficult. Besides, minor elevation in transaminases qualified as DILI might, indeed, represent adaptive, non-progressive changes rather than true hepatotoxicity. The differences observed in clinically not robust primary efficacy estimates, jointly with the aforementioned variability in DILI case qualification criteria, the need to properly characterise the underlying condition and stage of disease for enrolment [80], underscores the need of reaching an international consensus in the context of future clinical trials to standardise DILI case qualification, severity index criteria, and endpoints to evaluate the efficacy of novel interventions for exploring novel biomarkers in DILI.

Moreover, due to the lack of specific diagnostic tests and biomarkers, causality assessment of DILI relies on subjective expert consensus opinion. The use of the RUCAM scale as a validated liver-specific scale should be a valid instrument in causality assessment of DILI [81,82].

This study has several strengths. This is the first attempt to perform a systematic review of clinical trials designed for prevention and management of idiosyncratic DILI. Further, we performed an extensive literature search in six different databases. Nonetheless, an inherent weakness is the inability of including unfinished or unpublished trials. However, to overcome this limitation, we performed a search in grey

literature to identify these trials. Another limitation is that, despite our complete search, our quantitative analyses are underpowered due to the scarcity of clinical trials. Further, some of the trials included, due to its methodological design and quality, would have exaggerated intervention effects [24] and consequently our findings should be interpreted cautiously.

5. Conclusions

This systematic review illustrates the difficulties and deficiencies of clinical research on DILI, due to the rarity of the condition and heterogeneity of the manifestations, which have led some authors to consider that RCTs for DILI are too challenging and often inconclusive. In addition, due to its low frequency, investment in preventing DILI is hard to justify. A risk-benefit analysis would tend to discount prophylaxis due to questions around cost effectiveness and safety, except for patients undergoing anti-TB or anti-cancer therapy in addition to other vulnerable populations. There is a need for planning and execution of coordinated multicentre clinical trials in DILI aimed at investigating the effectiveness of known and novel interventions that could improve clinical outcomes of DILI within the framework of adaptive clinical trial design. These trials would need to define threshold criteria for patient inclusion and sample sizes to ensure adequate statistical power, together with monitoring plans, stopping criteria and precisely-defined endpoints.

Guarantor of article

M Isabel Lucena.

Author contributions

HN, JSC, IAA and MIL contributed to the conception and design of the systematic review and meta-analysis. HN, JSC, IAA and MIL contributed to the initial electronic literature search, study eligibility assessment, data extraction and quality and risk of bias assessment, and analysis and interpretation. HN, JSC and IAA drafted the manuscript. MRD, SS, GPA, ESB, RJA and MIL critically revised the manuscript. All authors approved the final version of the manuscript.

Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phrs.2020.105404.

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